REMARKS

Claims 2, 4, 15 and 16 have been cancelled, and claim 1 amended to more definitely set forth the invention and obviate the rejections. Support for the amendment of claim 1 can be found in the specification on page 6, line 18, and page 9, lines 2-9, and in Examples 3-10 on pages 34-43. This amendment is deemed not to add new matter. Claims 1, 3, 5-14 and 17 are in the application, claim 13 having been withdrawn from consideration.

Reconsideration is respectfully requested of the rejection of claims 1-4 and 14-16 under 35 U.S.C. 103(a) as being unpatentable over JP 08-325149 in view of Obayashi, et al. (4,880,888).

The cited primary '149 reference is concerned with a pridinol mesylate external preparation, used as a skeletal muscle relaxant, administered via percutaneous absorption (through the skin). In addition to pridinol mesylate, the external preparation contains other components, such as glycerin, ethylene glycol, etc. Importantly, the active ingredient pridinol is administered via pridinol mesylate, NOT as pridinol in free form, as now claimed in the present application.

Further, as the Examiner has admitted on page 3, line 8 of the instant Office Action, the '149 reference fails to teach the polyfunctional epoxy compound or crosslinking agents claimed herein. To cure these deficiencies, the Examiner has cited the Obayashi, et al. reference. The Obayashi, et al. reference teaches a process for producing a water-absorbent resin. The Obayashi, et al. reference does disclose polyacrylic acids and diglycidyl compounds, but fails to disclose that the polyfunctional epoxy compound is for use in the donor gel as herein. Rather, the Obayashi, et al. reference states that the polyfunctional epoxy compounds are crosslinking agents

that react with carboxyl groups present in the α, β-unsaturated carboxylic acid and its alkali metal salt or their polymer (see column 4, lines 59, through column 5, line 7).

In contrast, the present invention, as now claimed in amended claim 1, provides an adhesive gel composition for an iontophoresis comprising:

(a) one or more basic drug(s) **in free form**,

(b) an acidic polymer,

(c) a poly-functional epoxy compound,

(d) water,

(e) a polyhydric alcohol; and/or

(f) a gelatin,

wherein a weight ratio of the basic drug(s) in free form to the acidic polymer is in a range of from 2:1 to 1:3.

Importantly, the present inventors unexpectedly discovered that, by adjusting the weight ratio of the acidic polymer to the basic drug, an iontophoresis composition having excellent moldability and adhesive performance could be obtained WITHOUT reducing the drug delivery rate. Further, it was unexpectedly discovered that a basic drug in a free form could be administered more effectively than conventional techniques (such as by administering pridinol mesylate, as disclosed in the '149 reference).

In particular, it was unexpectedly discovered that, "by adding a free form of a basic drug to neutralize the carboxyl group of a base polymer, it becomes possible to suppress a reduction in the cohesive force without the need of any additives such as a pH modifier, to increase the pH, to reduce the skin irritating effect and to reduce the competition between the drug and a hydrogen

ion upon energization of an iontophoresis, whereby increasing the permeability of the drug". (see Specification, page 9, lines 2-9).

In addition, the present inventors unexpectedly discovered that a polyfunctional epoxy compound provides exceptional crosslinking effects when incorporated into the donor gel of the present invention comprising the basic drug in free form. Specifically, "the addition of a polyhydric alcohol increases the cohesive force, the water-retaining ability and the drug solubility of an adhesive composition" (Specification, page 9, lines 10-12).

It has been unexpectedly discovered by the present inventors that, by providing the basic drug in free form and acidic polymer in the adhesive gel composition of the present invention within a ratio of from 2:1 to 1:3 as shown in, for example, Examples 3-10, excellent moldability and adhesive performance of the gel, as well as efficient diffusion and the release of the drug, can be obtained. The combination of said basic drug in free form and acidic polymer in such a claimed ratio allows adjustment of the pH of the base polymer (i.e., acidic polymer in the adhesive gel composition) to be within a weakly acidic to neutral range, thus providing suitable gel moldability and adhesive performance.

Proof of an unexpected improvement can rebut a *prima facie* case of obviousness. *In re Murch* 464 F2d 1051, 175 USPQ 89 (CCPA 1972); *In re Costello* 480 F2d 894, 178 USPQ 290 (CCPA 1973). It was unexpectedly discovered by the present inventors that, by providing the basic drug **in free form** and acidic polymer in the adhesive gel composition of the present invention **within a ratio of from 2:1 to 1:3** as shown in, for example, Examples 3-10, unexpectedly improved moldability and adhesive performance of the gel, as well as efficient diffusion and the release of the drug, can be obtained. The combination of said basic drug in free

form and acidic polymer in such a claimed ratio allows adjustment of the pH of the base polymer (i.e., acidic polymer in the adhesive gel composition) to be within a weakly acidic to neutral range, thus providing suitable gel moldability and adhesive performance.

The cited references, either alone or in combination, fail to disclose the use of the basic drug in free form, the unexpected results obtained when providing the basic drug to acidic polymer in the claimed ratio, or the unexpected improvement in moldability, adhesive performance of the gel, efficient diffusion and the release of the drug obtained with the composition of the present invention. Rather, these teachings come only from the present invention, and constitute important elements or aspects thereof.

In view of the deficiencies of the prior art as stated above, the unexpected improvements found with the now claimed combination herein, and the legal authority cited above, it is believed that the Examiner would now be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 6-12 and 17 under 35 U.S.C. 103(a) as being unpatentable over JP 08-325149 in view of Obayashi, et al. (4,880,888), and further in view of Sage, et al. (USP 5,540,669).

The '149 and '888 references are discussed in detail above. As stated by the Examiner, neither of these cited references discloses a mixture of lidocaine and epinephrine, as claimed herein claims 6-12 and 17. To cure said deficiency, the Examiner has cited the Sage, et al. reference. The Sage, et al. reference discloses an iontophoretic drug delivery system and method for using same, wherein lidocaine and epinephrine are administered via iontophoresis.

However, the present inventors discovered that an iontophoresis composition could be

provided comprising an acidic polymer, and a combination of lidocaine and epinephrine, in the claimed ratio, to provide a "shorter-acting effect, an increased effect and a prolonged effect. This is attributable to an efficient absorption of a drug due to less competitive ion species existing in a base in a base composition of the present invention" (see Specification, page 17, lines 11-16).

In particular, the present inventors discovered that, by lowering the pH and adding a component to prevent oxidation, epinephrine could be stabilized and protected from oxidation (see page 19, lines 2-6). "To adjust the pH and the adhesive performance "..."is preferable also in view of the handling, the practicality and the viscosity upon manufacturing, since the skin irritating effect is reduced and a suitable adhesion performance can be obtained" (see Specification, page 18, lines 10-14). The cited Sage, et al. reference fails to disclose the use of antioxidants to prevent the oxidation and degradation of the epinephrine, as disclosed herein. Further, the combination of cited references fails to teach an adhesive gel composition containing a basic drug in free form, nor the unexpected results obtained from providing the drug and the polymer in the ratio now claimed in claim 1 herein.

In view of the deficiencies of the prior art and the amendments made to the claims herein, it is believed that the instant rejection now fails. As such, withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 1-5 and 14-16 under 35 U.S.C. 103(a) as being unpatentable over Oda, et al. (5,725,874).

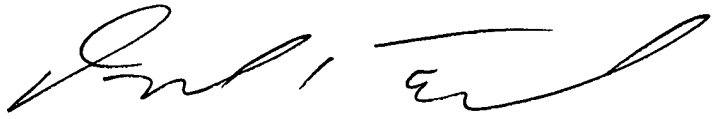
The Oda, et al. reference discloses a solubilizer and external preparation containing same, wherein a solubilizer is provided with improved solubilizability for pharmaceutically effective ingredients, for use in percutaneously absorbable preparations.

However, it is believed that the '874 reference fails to disclose the ratio of the basic drug to acid polymer, as now claimed herein. Moreover, in the formulation disclosed in the '874 reference, the drug is dissolved in the solubilizing agent (the oily phase), such that the electromotive force cannot affect the drug. Thus, in contrast to the present invention, such a composition as disclosed in the Oda, et al. reference cannot be utilized as the donor gel in iontophoresis.

Further, it is believed that the cited Oda, et al. reference fails to disclose the claimed ratio of basic drug to acidic polymer, as now claimed herein, which provides unexpectedly improved results as described above. In view of the deficiencies of the Oda, et al. reference, the amendments to claim 1 made herein, and the unexpected improvements obtained with the combination of elements claimed in the composition of the present invention, it is believed that the Examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

In view of the foregoing, it is respectfully submitted that the application is now in condition for allowance, and early action and allowance thereof is accordingly respectfully requested. In the event there is any reason why the application cannot be allowed at the present time, it is respectfully requested that the Examiner contact the undersigned at the number listed below to resolve any problems.

Respectfully submitted,



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